REMARKS/ARGUMENTS

Claims 1-11 were pending in this application. According to the July 21, 2003 Office Action, claims 1-11 were rejected.

Rejection under 35 U.S.C. §102

The Examiner rejected claims 1-3 under 35 U.S.C. §102(b) as allegedly being anticipate by Biogram AB.

In response, Applicants respectfully traverse the Examiner's rejection. The present invention relates to a pharmaceutical preparation of microcapsules of lactic-co-glycolic copolymer which incorporates a peptide of pharmaceutical interest, characterized in that the copolymer that forms the microcapsules incorporates a citric acid ester as an additive **and the peptide is not present on the surface of the microcapsule**.

In contrast, WO97/14408 discloses a drug delivery system described as a microcapsule consisting of a starch nucleus, incorporating a protein type drug (and therefore, having a much higher molecular weight than a peptide), and a coating of lactic-co-glycolic polymer. This reference does not specify that the peptide is not present on the surface of the microcapsule. In addition, the microparticle of WO97/14408 consists of a starch nucleus that contains the biologically active substance, where said nucleus is coated by a polymer that may contain additives), whereas the microcapsules of the present invention do not contain any starch nucleus where the biologically active peptide is dispersed. Accordingly, the Examiner is kindly requested to withdraw this rejection

Rejection under 35 U.S.C. §103

The Examiner rejected claims 4 and 5 under 35 U.S.C. §103(a) as allegedly being unpatentable over Biogram AB. The Examiner also rejected claims 6-11 under 35 U.S.C. §103(a) as allegedly being unpatentable over Biogram AB in view of Yamamoto et al., Bodmer et al. and Canal et al.

In response, Applicants respectfully traverse the Examiner's rejection and reiterate the comments made with regard to the rejection under Section 102 above. Furthermore, Applicants note that the incorporation of drugs, particularly peptides and proteins inside microparticles formed by lactic-co-glycolic polymer is well known. The incorporation of additives together with the drug and/or the polymer is also known since long, as may be verified in the reading of, for example, U.S. Patent Nos. 3,773,919 and 4,675,189.

Nevertheless, the release of the incorporated drugs in these systems (i.e., the way they are released) depends upon multiple factors, as for example the manufacturing process, the composition and the shape of the encapsulation system, the molecular weight of the polymer used, the molecular weight of the encapsulated drug, the ratio between monomers in the polymer, the ratio between the encapsulated drug and the polymer, or the presence of additives in the polymer (see U.S. Patent Nos. 3,887699, 4,767,628 and 4,675,189). The release is also strongly influenced by the structure and intimate composition of the particle. Accordingly, a particle containing the drug uniformly distributed throughout the particle; a particle of drug being coated with the polymer; a particle constituted by a nucleus formed by an inert substance (for example starch or gelatine) incorporating the drug, said nucleus in turn being coated by the polymer, are completely different from one of another. For example, it is different having a capsule wherein the coating encloses directly a solid or liquid drug particle, or having a capsule wherein the coating encloses a mixture of a drug and another substance, or having a capsule wherein the coating encloses another microcapsule.

Indeed, all these particles are modifications of the same combination of polymer, drug and additives. The use of a particular additive or even the combinations of drug and polymer, are not at all obvious, as in this kind of products the main parameter for determining the quality of these systems in their final (industrial) application will be the profile of the release of the drug (the way of the release, its speed...) entrapped inside of the encapsulation system; this way of release always depends on the particular combination of drug + polymer + additive + manufacturing process.

Accordingly, the use of some plasticizers as tributyl citrate, tetrabutyl citrate, isopropyl myristate, acetilated monoglicerides, triacetine, or diethyl phtalate, **in microcapsules of lactic-co-glycolic polymers**, incorporating non-peptidic drugs, **is described as producing an increase of the release profile of the encapsulated drug**. See Pill et al., Sustained drug delivery systems. I. The permeability of poly(e-caprolactone), poly (DL-lactic acid), and their copolymeres. Journal of Biomedical Materials Research, 13, pages 497-507 (1979); Sansdrap P. et al.,"Influence Of Additives On The Release Profile Of Nifedipine From Poly (Dl-Lactide-Co-Glycolide) Microspheres", Journal of Microencapsulation vol. 15, n° 5, pages.545-553 (1998); and Wang et al., "In Vitro And In Vivo Evaluation Of Taxol Release From Poly(Lactic-Co-Glycolic Acid) Microspheres Containing Isopropyl Miristate And Degradation Of Microspheres", Journal of Controlled Release, 49, pages. 157-166 (1997),

In contrast, **in the microcapsules according to the present patent application the effect is exactly the opposite**, that is, **the present combination of citric acid esters + polymer + peptide**, surprisingly, **produces a reduction of** the initial release of the peptide when increasing the concentration of citric acid esters in the microcapsules. Hence, the importance of not having a peptide on the surface of the microcapsule, a property that is not specifically disclosed or suggested by any of the cited prior art alone or in combination

Furthermore, WO97/14408 discloses that microcapsules may optionally incorporate additives described in an extensive list, wherein the triethyl citrate is apparently included merely in a speculative manner, as it is not further mentioned in any example of this patent publication. There are no indication of the particular advantage that only a citric acid ester is able to provide in reducing the initial release of the peptide.

Furthermore and as it relates to claim 6 of the present invention, WO97/14408 refers to the use of proteins which are solvent sensitive, i.e sensitive to organic solvents (see page 11, lines 24 to 32), which is not the case of the analogues of LHRH (see present claim 6), as these analogues are obtained by synthesis in an organic solvent, as is shown for example in

WO00/71570 or US Patent No. 6,346,601).

WO97/14408 describes the use of additives incorporated into the polymer dividing them in two main groups (see page 10, lines 29-36):

- The first of these groups comprises "film property modifying agents", which includes plasticizers, and wherein one citric acid ester is mentioned, in particular the triethylcitrate.

- The second of these groups comprises "release controlling agents", wherein a wide range of substances are cited, for example acids, bases.... these substances are said to have the capacity of modifying the manner the encapsulated drug is released. No citric acid ester is mentioned in this group.

It has now surprisingly been found that the citric acid esters (particularly the triethylcitrate) acts as a "release controlling agent", and accordingly aids to modify the drug release parameters of the microcapsules, and surprisingly, this modification is the contrary as expected from the prior art documents, as mentioned before.

As indicated before, the drug release properties of a certain microcapsule are not only dependent upon its composition (drug + polymers + additives), but also upon the intrinsic structure of said microcapsules, which will be determined by the manufacturing process by which they are obtained. The final properties of the drug release system will be completely dependent upon the combination of said parameters. In the presently claimed microcapsule, the use of a citric acid ester and the lack of presence of peptide on the surface of the microcapsule are key parameters for the success of the present invention above. These properties are not disclosed or suggested in any of the cited references alone or in combination. Accordingly, the Examiner is kindly requested to withdraw this rejection.

In light of the foregoing, it is respectfully submitted that this application is now in condition to be allowed and the early issuance of a Notice of Allowance is respectfully solicited. If there are any issues or amendments the Examiner wishes to discuss, the Examiner is encouraged to contact the undersigned.

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on December 11, 2003:

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Respectfully submitted,

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